Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claims 1-81 (canceled)

Claim 82. (currently amended) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing a sample comprising the target nucleic acid to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

(1) a first probe set comprising a plurality of different probes, each probe exactly complementary to a subsequence of the reference sequence, the probe including a single interrogation position complementary to a corresponding nucleotide in the reference sequence, wherein the reference sequence is at least 50 bases, and the different probes of the first probe set are overlapping probes spanning the reference sequence;

(2) a second probe set comprising a corresponding probe for each of the different probes in the first probe set, the corresponding probe in the second probe set being identical to the corresponding probe from the first probe set that includes the interrogation position, except that the one interrogation position is occupied by a different nucleotide in each of the two corresponding probes from the first and second probe sets;

wherein~~, the different probes in the first probe set have at least three interrogation positions respectively corresponding to each of at least three contiguous nucleotides in the reference sequence~~ the first probe set comprises at least three different interrogation positions corresponding to respective nucleotides in the reference sequence, the respective nucleotides forming at least three continguous nucleotides in the reference sequence, and

(b) detecting a hybridization pattern of the oligonucleotide probes to the target nucleic acid and determining from the hybridization pattern whether a nucleotide in the target sequence is the same or different from the corresponding nucleotide in the reference sequence.

Claim 83. (previously presented) The method of claim 82, wherein the determining comprises comparing the hybridization pattern to the target nucleic acid with a hybridization pattern of a nucleic acid having the reference sequence to the array of oligonucleotide probes.

Claim 84. (previously presented) The method of claim 82, wherein the determining step comprises:

(1) comparing the relative specific binding of two corresponding probes from the first and second probe sets;

(2) assigning a nucleotide in the target sequence as the complement of the interrogation position of the probe having the greater specific binding;

(3) repeating (1) and (2) until each nucleotide of interest in the target sequence has been assigned.

Claim 85. (currently amended) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing a sample comprising the target nucleic acid to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

(1) a first probe set comprising a plurality of different probes, each probe exactly complementary to a subsequence of the reference sequence, the probe including a single interrogation position complementary to a corresponding nucleotide in the reference sequence,

(2) second, third and fourth probe sets, each comprising a corresponding probe for each of the different probes in the first probe set, the corresponding probes in the second, third and fourth probe sets being identical to the corresponding probe from the first probe set that includes the interrogation position, except that the interrogation position is occupied by a different nucleotide in each of the four corresponding probes from the first, second, third and fourth probe sets;

wherein~~, the different probes in the first probe set have at least three interrogation positions respectively corresponding to each of at least three contiguous nucleotides in the reference sequence~~ the first probe set comprises at least three different interrogation positions corresponding to respective nucleotides in the reference sequence, the respective nucleotides forming at least three continguous nucleotides in the reference sequence, and

(b) detecting a hybridization pattern of the oligonucleotide probes to the target nucleic acid and determining from the hybridization pattern whether a nucleotide in the target sequence is the same or different from the corresponding nucleotide in the reference sequence.

Claim 86. (previously presented) The method of claim 85, wherein the determining comprises comparing the hybridization pattern of the target nucleic acid with a hybridization pattern of a nucleic acid having the reference sequence to the oligonucleotide probes.

Claim 87. (previously presented) The method of claim 85, wherein the determining comprises:

(1) comparing the relative specific binding of four corresponding probes from the first, second, third and fourth probe sets;

(2) assigning a nucleotide in the target sequence as the complement of the interrogation position of the probe having the greatest specific binding;

(3) repeating (1) and (2) until each nucleotide of interest in the target sequence has been assigned.

Claim 88. (previously presented) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing the target nucleic acid to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

a perfectly matched probe exactly complementary to a subsequence of a reference sequence, the perfectly matched probe having a plurality of interrogation positions respectively corresponding to a plurality of nucleotides in the reference sequence,

for each interrogation position, three mismatched probes, each identical to the perfectly matched probe including the plurality of interrogation positions, except in the interrogation position, which is occupied by a different nucleotide in each of the three mismatched probes and the perfectly matched probe;

(b) for each interrogation position,

(1) comparing the relative specific binding of the three mismatched probes and the perfectly matched probe;

(2) assigning a nucleotide in the target sequence as the complement of the interrogation position of the probe having the greatest specific binding.

Claim 89. (previously presented) The method of claim 88, wherein the target sequence has an undetermined substitution relative to the reference sequence, and the method assigns a nucleotide to the substitution.

Claim 90. (currently amended) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

hybridizing the target sequence to an array of oligonucleotide probes immobilized on a solid support, the array comprising at least one pair of first and second probe groups, each group comprising a first and second sets of oligonucleotide probes,

the first probe set comprising a plurality of different probes, each probe exactly complementary to a subsequence of a reference sequence, the ~~segment~~ probe including a single interrogation position complementary to a corresponding nucleotide in the reference sequence, wherein the reference sequence is at least 50 bases, and the different probes of the first probe set are overlapping probes spanning the reference sequence;

the second probe set comprising a corresponding probe for each of the different probes in the first probe set, the corresponding probe in the second probe set being identical to the corresponding probe from the first probe set, except that the interrogation position is occupied by a different nucleotide in each of the two corresponding probes from the first and second probe sets;

wherein ~~the probes in the first probe set have at least three interrogation positions respectively corresponding to each of three contiguous nucleotides in the reference sequence~~ the first probe set comprises at least three different interrogation positions corresponding to respective nucleotides in the reference sequence, the respective nucleotides forming at least three continguous nucleotides in the reference sequence;

wherein each of the different probes in the first probe set from the first group is exactly complementary to a subsequence of a first reference sequence and each of the different probes in the first probe set from the second group is exactly complementary to a subsequence from a second reference sequence;

determining which probes in the first group, relative to one another, hybridize to the target sequence, the relative specific binding of the probes indicating whether the target sequence is the same or different from the first reference sequence;

determining which probes in the second group, relative to one another, hybridize to the target sequence, the relative specific binding of the probes indicating whether the target sequence is the same or different from the second reference sequence.

Claim 91. (previously presented) The method of claim 90, wherein the hybridizing step comprising hybridizing the target sequence and a second target sequence to the array, and the relative specific binding of the probes from the first group indicates that the target is identical to the first reference sequence, and the relative specific binding of the probes from the second group indicates that the second target sequence is identical to the second reference sequence.

Claim 92. (previously presented) The method of claim 90, wherein the first and second target sequences are heterozygous alleles.

Claim 93. (previously presented) The method of claim 82, wherein the probes are 6-30 nucleotides long.

Claim 94. (previously presented) The method of claim 90, wherein the probes are 6-30 nucleotides long.

Claim 95. (new) A device for detecting at least one variation in the splicing of a gene comprising

an array of nucleic acid probes immobilized on a solid support, the array comprising at least two sets of probes of between 3 and 100 nucleotides in length,

wherein said array comprises at least a first and a second probe arranged on the solid support,

wherein said first probe comprises a first sequence that is complementary to an exon or an intron of a gene, and wherein said sequence corresponds to at least one region of variation corresponding to a splice sequence, and

wherein said second probe comprises a second sequence that is complementary to an exon-intron boundary of said gene, and wherein said second sequence corresponds to at least one region of variation corresponding to a splice sequence,

said device allowing, when hybridized with a target sequence, detection of the presence or absence of said at least one variation in the splicing of a gene.

Claim 96. (new) The device of claim 95, wherein said probe sequences are publicly available.

Claim 97. (new) The device of claim 95, wherein the probes are immobilized on a chip.

Claim 98. (new) The device of claim 95, wherein said probes are oligodeoxyribonucleotides or oligoribonucleotides.

Claim 99. (new) The device of claim 95, wherein said probes comprise sequences of between 3 and 50 nucleotides.

Claim 100. (new) The device of claim 95, wherein said first and second probes exhibit complementarity to reference sequences comprising mutations or polymorphisms associated with phenotypic changes having clinical significance in human patients.

Claim 101. (new) The device of claim 100, wherein said first and second probes exhibit complementarity to reference sequences comprising mutations or polymorphisms associated with cancer.

Claim 102. (new) A method of producing a device comprising an array of nucleic acid probes immobilized on a solid support, the array comprising at least two sets of probes of between 3 and 100 nucleotides in length,

(a) providing said nucleic acid probes, wherein said probes comprise at least a first and a second probe,

wherein said first probe comprises a first sequence that is complementary to an exon or an intron of a gene, and wherein said sequence corresponds to at least one region of variation corresponding to a splice sequence, and

wherein said second probe comprises a second sequence that is complementary to an exon-intron boundary of said gene, and wherein said second sequence corresponds to at least one region of variation corresponding to a splice sequence; and

(b) arranging and immobilizing said first and second probes on the solid support,

said device allowing, when hybridized with a target sequence, detection of the presence or absence of said at least one variation in the splicing of a gene.

Claim 103. (new) The method of claim 102, wherein said first or second probe is obtained by:

(a) identifying at least two nucleic acid sequences corresponding to a splice sequence and a mutation in a splice sequence, respectively, wherein said mutation has a phenotypic effect of clinical significance, and

(b) synthesizing nucleic acid probes containing complementarity to said splice sequence.

Claim 104. (new) The method of claim 102, wherein said probe sequences are publicly available.

Claim 105. (new) The method of claim 102, wherein the probes are immobilized on a chip.

Claim 106. (new) The method of claim 102, wherein said first and second probes exhibit complementarity to reference sequences comprising mutations or polymorphisms associated with phenotypic changes having clinical significance in human patients.

Claim 107. (new) The method of claim 106, wherein said first and second probes exhibit complementarity to reference sequences comprising mutations or polymorphisms associated with cancer.

Claim 108. (new) The method of claim 102, wherein said probes comprise sequences of between 3 and 50 nucleotides.

Claim 109. (new) The device of claim 95, wherein said device allows detection of the presence or absence of said at least one variation in the splicing of a gene in an mRNA population.

Claim 110. (new) The device of claim 95, wherein said device allows detection of the presence or absence of at least one variation in the splicing of more than one gene.

Claim 111. (new) A device for identifying at least one differentially spliced gene product, wherein said device comprises

a solid support material and single-stranded oligonucleotides of between 5 and 100 nucleotides in length attached to said support material,

wherein said oligonucleotides comprise at least a first and a second

oligonucleotide molecule arranged serially on the support material,

wherein said first oligonucleotide molecule comprises a first sequence that is complementary to and specific for an exon or an intron of a first gene, and wherein said first sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing, and

wherein said second oligonucleotide molecule comprises a second sequence that is complementary to and specific for an exon-exon or exon-intron junction region of said first gene, and wherein said second sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing,

said device allowing, when contacted with a sample containing at least one nucleic acid molecule under conditions allowing hybridisation to occur, the determination of the presence or absence of said differentially spliced gene product.

Claim 112. (new) The device of claim 111, wherein said first and second oligonucleotide molecules are available from a compilation of published sequences or sequence information from at least one database.

Claim 113. (new) The device of claim 111, wherein the support material is selected from the group consisting of a filter, a membrane and a chip.

Claim 114. (new) The device of claim 111, wherein said single-stranded oligonucleotides are RNA or DNA molecules.

Claim 115. (new) The device of claim 111, wherein said single-stranded oligonucleotides comprise oligonucleotides of less than 50 nucleotides in length.

Claim 116. (new) The device of claim 111, wherein said single-stranded oligonucleotides are specific for alternative splicings representative of a cell or tissue in a given pathological condition.

Claim 117. (new) The device of claim 116, wherein said single-stranded oligonucleotides are specific for alternative splicings representative of a tumor cell or tissue.

Claim 118. (new) The device of claim 116, wherein said single-stranded oligonucleotides are specific for alternative splicings representative of a cell or tissue undergoing apoptosis.

Claim 119. (new) The device of claim 111, where said device is useful to evaluate the toxicity of a compound or treatment to a cell, tissue, or organism by determining the presence or absence of said differentially spliced gene product in a sample treated with said compound or treatment.

Claim 120. (new) The device of claim 111, where said device is useful to evaluate the therapeutic efficacy of a compound to a cell, tissue, or organism by determining the presence or absence of said differentially spliced gene product in a sample from said cell, tissue, or organism.

Claim 121. (new) The device of claim 111, where said device is useful to evaluate the responsiveness of a subject to a compound or treatment by determining the presence or absence of said differentially spliced gene product in a sample from said subject exposed to said compound or treatment.

Claim 122. (new) A method of producing a device comprising a support material and single-stranded oligonucleotide of between 5 and 100 nucleotides in length attached to said solid support material, wherein said method comprises:

(a) providing said oligonucleotides, wherein said oligonucleotides comprise at

least a first and a second oligonucleotide molecule,

wherein said first oligonucleotide molecule comprises a first sequence that is complementary to and specific for an exon or an intron of a first gene, and wherein said first sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing, and

wherein said second oligonucleotide molecule comprises a second sequence that is complementary to and specific for an exon-exon or exon-intron junction region of said first gene, and wherein said second sequence corresponds to a region of variability in at least one product of said first gene due to differential splicing; and

(b) arranging and immobilizing said oligonucleotides serially on said support material,

said device allowing, when contacted with a sample containing at least one nucleic acid molecule under conditions allowing hybridisation to occur, the determination of the presence or absence of at least one differentially spliced gene product.

Claim 123. (new) The method of claim 122, wherein said first or second oligonucleotide molecule is obtained by a method comprising:

(a) identifying at least two different oligonucleotides corresponding to a differentially spliced domain of a gene, wherein said differentially spliced domain is characteristic of a physiopathological condition, and

(b) synthesizing one or several single-stranded oligonucleotides complementary to and specific for said domain or a junction region formed by the splicing or absence of splicing of said domain.

Claim 124. (new) The method of claim 123, wherein the identification step (a) comprises:

i) hybridizing a plurality of different RNA or cDNA molecules derived from a first sample, wherein the composition or sequence of the RNA or cDNA molecules is at least

partially unknown, with a plurality of different cDNA molecules derived from RNA molecules of a second sample, wherein the composition or sequence of the cDNA molecules is at least partially unknown; and

ii) identifying, from the hybrids formed in i), a population of nucleic acid molecules comprising an unpaired region, wherein said unpaired region corresponds to a region of a gene that is differentially spliced between said first and second sample.

Claim 125. (new) The method of claim 122, wherein said first and second oligonucleotide molecules are obtained from a compilation of published sequences or sequence information from databases.

Claim 126. (new) The method of claim 122, wherein the support material is selected from a filter, a membrane, and a chip.

Claim 127. (new) The method of claim 122, wherein said single-stranded oligonucleotides are specific for alternative splicings representative of a cell or tissue in a given pathological condition.

Claim 128. (new) The method of claim 127, wherein said single-stranded oligonucleotides are specific for alternative splicings representative of a tumor cell or tissue.

Claim 129. (new) The method of claim 127, wherein said single-stranded oligonucleotides are specific for alternative splicings representative of a cell or tissue undergoing apoptosis.

Claim 130. (new) The method of claim 122, wherein said single-stranded oligonucleotides comprise oligonucleotides of less than 50 nucleotides in length.

Claim 131. (new) The device of claim 111, wherein said device allows the determination of the presence or absence of two or more differentially spliced gene products of said first gene.

Claim 132. (new) The device of claim 111, wherein said device allows the determination of the presence or absence of one or more differentially spliced gene products of two or more genes.

Claim 133. (new) The device of claim 95, wherein the first and second probes are arranged adjacent to one another on the solid support,